Dementia and dependence

Do modifiable risk factors delay disability?

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ABSTRACT

Objective: To identify modifying factors that preserve functional independence among individuals at high dementia risk.

Methods: Health and Retirement Study participants aged 65 years or older without baseline activities of daily living (ADL) limitations (n = 4,922) were interviewed biennially for up to 12 years. Dementia probability, estimated from direct and proxy cognitive assessments, was categorized as low (i.e., normal cognitive function), mild, moderate, or high risk (i.e., very impaired) and used to predict incident ADL limitations (censoring after limitation onset). We assessed multiplicative and additive interactions of dementia category with modifiers (previously self-reported physical activity, smoking, alcohol consumption, depression, and income) in predicting incident limitations.

Results: Smoking, not drinking, and income predicted incident ADL limitations and had larger absolute effects on ADL onset among individuals with high dementia probability than among cognitively normal individuals. Smoking increased the 2-year risk of ADL limitations onset from 9.9% to 14.9% among the lowest dementia probability category and from 32.6% to 42.7% among the highest dementia probability category. Not drinking increased the 2-year risk of ADL limitations onset by 2.1 percentage points among the lowest dementia probability category and 13.2 percentage points among the highest dementia probability category. Low income increased the 2-year risk of ADL limitations onset by 0.4% among the lowest dementia probability category and 12.9% among the highest dementia probability category.

Conclusions: Smoking, not drinking, and low income predict incident dependence even in the context of cognitive impairment. Regardless of cognitive status, reducing these risk factors may improve functional outcomes and delay institutionalization. ***Neurology*® 2014;82:1543–1550**

GLOSSARY

ADL = activities of daily living; **CI** = confidence interval; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **HRS** = Health and Retirement Study; **IPW** = inverse probability weighting; **OR** = odds ratio.

Cognitive impairment causes losses in independence in daily activities,[1] which hasten institutionalization.[2] Little prior research has examined whether factors that delay disability in cognitively normal adults have similar benefits among the cognitively impaired.

We hypothesized that onset of impairments in functional independence among individuals with cognitive impairment may be substantially accelerated by modifiable individual risk factors. This hypothesis is rooted in understanding of disability as emerging when physical impairments in body functioning or structure occur and it is not possible to adopt environmental, behavioral, and instrumental accommodations to overcome these impairments (see figure 1).[3,4] Individual-level modifiers, such as physical inactivity, alcohol consumption, smoking, depression, and low household income, may influence both the development of physical impairments and patients' ability to use accommodations or coping strategies. Cognitive impairment may also affect basic activities of daily living (ADL) independence because it reduces the patient's ability to adopt accommodations

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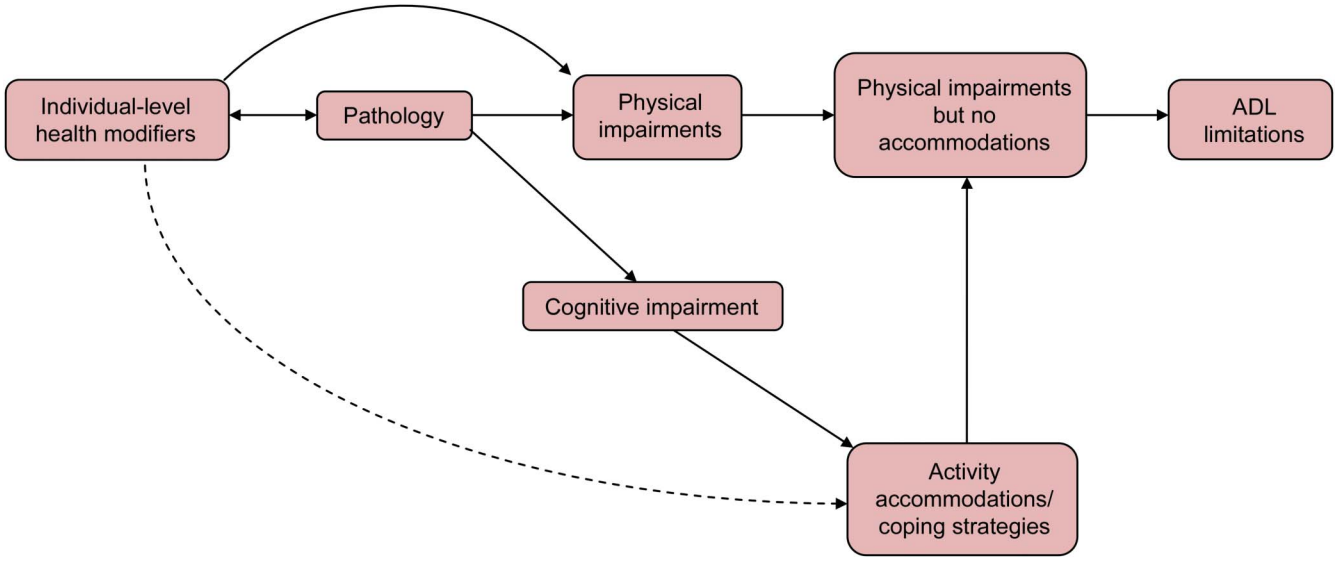
Figure 1 Hypothesized influence of individual-level health modifiers and cognitive impairment on the disablement process



An adaptation of the disablement process model by Verbrugge and Jette,[4] this figure illustrates how the co-occurrence of illness pathology and cognitive impairment leads to functional limitations and disability by impairing the patient's ability to adopt accommodations and coping strategies. ADL = activities of daily living.

or coping strategies. The combination of individual modifying risk factors and cognitive status will determine whether the patient is able to successfully use activity accommodations to interrupt the translation of physical impairments into ADL limitations. Assessing whether these individual risk factors modify the translation of cognitive impairments into disability has clinical importance because many of these factors may be insufficiently managed among patients with dementia.[5]

METHODS The Health and Retirement Study (HRS) is a nationally representative longitudinal survey of Americans aged 50 years or older and their spouses.[6,7] Participants were enrolled in 1992, 1993, and 1998 and were interviewed biannually through 2010.

Standard protocol approvals, registrations, and patient consents. The HRS was approved by the University of Michigan Health Sciences Human Subjects Committee. These analyses were determined exempt by the Harvard School of Public Health Office of Human Research Administration.

Outcome assessment. The outcome for this study was self-reported or proxy-reported (approximately 4% per wave) difficulty in 5 ADL (getting across a room, dressing, bathing, eating, and getting in and out of bed) in the past 30 days. Possible response options were yes, no, or do not do, which was treated as missing in this analysis. We looked at each activity individually and also used an indicator for any activity limitation, capturing limitations in any of the 5 ADL (based on the RAND HRS coding[8]).

Exposure status. Our primary exposure was imputed dementia probability score, a measure of cognitive impairment. Methods for calculating this score have been described in detail elsewhere.[9] Briefly, for participants too impaired to participate in interviews (approximately 2% per wave), proxies completed the Jorm Informant Questionnaire for Cognitive Decline and a single-item memory impairment question. Respondents able to participate in interviews completed immediate and delayed recall of 10-word lists and a modified Telephone Interview for Cognitive Status. In a subsample of participants, these items were combined and calibrated against dementia diagnosis according to *DSM-III-R* and *DSM-IV* criteria (C statistic = 94.3%). The dementia probability score corresponds to the estimated probability that the individual had dementia at interview per this calibration. For our analyses, the dementia probability score was divided into 4 categories (0 to ≤0.25, 0.25 to ≤0.50, 0.50 to ≤0.75, and 0.75 to ≤1), which represent low, mild, moderate, and high probability of developing dementia. The category of 0 to ≤0.25 (normal cognitive function) was used as the reference group for all analyses. In our longitudinal analyses, dementia probability score was assessed in the wave before ADL outcome assessment.

In secondary analyses, we used an imputed memory score as our measure of cognitive impairment and observed similar results (see appendix e-1 on the *Neurology*® Web site at Neurology.org).

Assessment of individual-level modifiers. We were interested in determining whether 5 self-reported or proxy-reported (approximately 2% per wave) individual-level factors (physical activity, drinking alcohol, smoking, depression, and income) predict similar reductions in the risk of incident ADL limitations regardless of level of cognitive impairment. Furthermore, we wanted to know whether these factors ameliorate or exacerbate the effects of cognitive impairment on incident ADL limitations, i.e., whether they interact with the cognitive impairment measures in predicting incident ADL limitations. Because of changes in the assessment of physical activity levels over time, physical activity was dichotomized as active vs inactive with active defined as vigorous activity ≥3 times per week in 1998 to 2002 and >1 time per week from 2004 onward (the closest available category to the previously used ≥3 times per week

cutpoint). Alcohol consumption was dichotomized into moderate drinking (more than 0 but fewer than 2 drinks per day) vs not drinking. Because of the low number of participants consuming 2 or more drinks per day, we excluded these individuals from our analyses of alcohol consumption, dementia category, and incident ADL limitations. Sensitivity analyses contrasting moderate drinkers with nonmoderate drinkers (nondrinkers or heavy drinkers) showed similar results to those presented here. Current smoking status was dichotomized (yes/no). An indicator variable for depression was constructed based on reporting ≥3 depressive symptoms on a modified 8-item Centers for Epidemiologic Studies–Depression Scale in the past 2 weeks. This threshold has been shown to have high sensitivity (71%) and specificity (79%) for depression per the Composite International Diagnostic Interview–Short Form.[10] We constructed an indicator variable for low income using a cutpoint of $12,031 (based on the 25th percentile of the household size–adjusted income at baseline). Modifier information was assessed in the wave before outcome assessment.

Covariates. We adjusted for the following potential time-constant confounders: age (centered, continuous), age squared, sex, race (black vs other), southern birthplace, education (modeled as linear terms for years of education with discontinuities at completion of high school and completion of college plus an indicator variable for GED completion), mother's and father's education (≤8 years vs >8 years), and height (sex-specific baseline quartiles). In addition, we adjusted for the following time-varying confounders: marital status (divorced/separated, widowed, never married, married), log of household size–adjusted wealth (continuous), body mass index (continuous), self-reported comorbidities (yes/no indicators for high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems, and arthritis), interview wave, and our modifiers. Time-constant confounders were assessed at study baseline (1998) and time-updated confounders were assessed at the wave before the exposure. Those missing information on any covariates at baseline were excluded from our analyses. If the covariate was missing during follow-up, the last reported value was carried forward.

Statistical analysis. Pooled logistic regression models were used to calculate odds ratios (ORs), which with rare outcomes approximates a hazard ratio as in continuous time survival analyses. The relationship of the dementia probability categories with risk of ADL limitations was approximately linear, so the categories were treated as a linear variable. Participants were censored from analysis after last interview, onset of activity limitations, death, or at first wave of missing information on dementia probability. We used inverse probability weighting (IPW) to adjust for potential time-varying confounding. IPW required one wave of "run-in" (see below), so our first "exposure" wave was in 2000 and our first "outcome" wave was in 2002. Those who reported ADL limitations in 1998 or 2000 were excluded from our analyses.

To assess whether any of our modifiers ameliorated or exacerbated the effects of dementia score on ADL limitations, 2 different approaches were used. First, we included an interaction term between dementia score category and each modifier (in separate models for each modifier) to test whether each modifier had different relative effects on ADL limitations depending on the participant's dementia score. Next, to compare the absolute effects of each modifier in participants with highest or lowest dementia score, we calculated the marginal probability of developing an activity limitation according to modifier status and dementia category. If effects of any risk factor are precisely multiplicative, the absolute benefit for individuals with cognitive impairment will be larger. These probabilities were calculated using the coefficients estimated in the logistic models with interaction terms and the actual population distribution of other covariates. The marginal probabilities were then compared based on the predicted population incidence rate of ADL limitations if everyone in the population had: (1) low dementia probability and the "beneficial" value of the modifier; (2) low dementia probability and the "adverse" value of the modifier; (3) high dementia probability and the "beneficial" value of the modifier; or (4) high dementia probability and the "adverse" value of the modifier. All analyses were performed using PROC SURVEYLOGISTIC in SAS 9.2 (SAS Institute, Cary, NC) and Stata 12 (StataCorp, College Station, TX) with weights as described below.

We used IPW to avoid introducing bias by adjusting for variables potentially affected by prior exposure but which affect future exposure. We constructed 4 weights: "treatment" (category of dementia score), modifier status (separate weights were calculated for each modifier), survival, and participation in HRS. These weights were multiplied to create a weight for each observation reflecting the inverse probability that the individual was alive and participated in the outcome wave, and had the dementia and modifier values he or she actually had, given past dementia, modifier, and covariate history. We additionally included the HRS sampling weight from 1998. Weights were stabilized[11] and truncated at the 98th percentile to minimize the influence of outliers.

We had 4,922 individuals eligible for our analysis of the association between dementia score and any ADL limitation (see figure e-1 for exclusions). For analyses of onset of specific ADL limitations, the exact number of individuals eligible differs slightly for each ADL because of differences in the baseline prevalence of each ADL limitation.

RESULTS Most respondents (94.2%) had low dementia probability at baseline (table 1) and throughout follow-up (table 2).

Higher dementia probability score category was associated with increased risk of incident ADL limitations, with a per-category OR of 1.65 (95% confidence interval [CI]: 1.49, 1.83) (results not shown). This implies that individuals with the highest dementia category (>75% probability of dementia) had 4.48 times the odds of onset of ADL limitations as individuals in the lowest dementia category (≤25% probability of dementia).

Table 3 shows the association between dementia probability category and risk of incident ADL limitations, the association between each modifier and incident ADL limitations, and the interaction coefficient between dementia probability and each modifier. In these models, an interaction coefficient of 1 indicates that the modifier has the same relative effect on ADL limitations regardless of dementia probability; if the interaction coefficient is less than 1, it indicates that the modifier effect is lower (less harmful) among those with higher dementia probability.

For the outcome of any ADL limitation, among the physically active, each unit increase in dementia

Table 1 Baseline characteristics of participants included in the analysis of dementia probability category and any incident activities of daily living limitations by dementia probability category at baseline

	Dementia probability category			
	0–0.25 (n = 4,636)	0.25–0.50 (n = 146)	0.50–0.75 (n = 65)	0.75–1 (n = 75)
Age, y, mean (SD)	72.4 (5.6)	80.0 (6.8)	81.2 (6.0)	80.6 (6.7)
Sex, % male	43.7	41.8	29.2	22.7
Race, % black	9.1	19.9	15.4	24.0
Southern birthplace, %	12.7	20.6	15.4	22.6
Years of education, mean (SD)	12.6 (2.8)	10.8 (3.5)	9.9 (3.4)	9.9 (3.9)
Mother had ≥8 y of education, %	53.0	45.9	36.9	33.3
Father had ≥8 y of education, %	45.5	41.1	30.8	33.3
Height, m, mean (SD)	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
Marital status, %				
Married	65.5	48.0	40.0	41.3
Divorced/separated	6.3	5.5	9.2	5.3
Widowed	24.7	43.2	49.2	52.0
Never married	3.5	3.4	1.5	1.3
Not physically active, %	51.3	63.7	69.2	84.0
Nondrinker, %	74.8	87.1	92.2	94.7
Current smoking, %	8.9	10.3	1.5	4.0
Current depression, %	9.3	19.2	13.9	17.3
Low household size-adjusted income, %	18.4	39.0	50.8	50.7
Body mass index, kg/m^2, mean (SD)	26.1 (4.2)	25.4 (4.0)	24.2 (4.4)	24.4 (4.0)
No. of comorbidities, mean (SD)	1.5 (1.2)	1.6 (1.1)	1.6 (1.3)	1.4 (1.2)

category was associated with an OR of 1.83 (95% CI: 1.36, 2.46). Low physical activity was associated with an increase in incident ADL limitations among those with the lowest dementia probability OR = 1.51 (95% CI: 1.25, 1.81). The interaction between physical activity and dementia probability was close to 1 and not significant (OR = 0.86; 95% CI: 0.63, 1.18), indicating that the estimated relative harm of low physical activity was similar regardless of dementia category. Depression was also associated with an increased risk of ADL limitations and the interaction between depression and dementia probability suggested that depression may be less harmful, in relative terms, among the cognitively impaired (OR = 0.72; 95% CI: 0.56, 0.92). Not drinking, smoking, and low income were not associated with an increased risk

Table 2 Distribution of dementia probability score and number of any incident ADL limitations by year

	Year					
	2002	2004	2006	2008	2010	Any incident ADL limitation
Dementia probability category, n (%)						
0–0.25	4,636 (94.2)	3,724 (93.7)	3,024 (93.1)	2,379 (92.3)	1,819 (91.8)	1,493 (80.2)
0.25–0.50	146 (3.0)	119 (3.0)	106 (3.3)	105 (4.1)	87 (4.4)	131 (7.0)
0.50–0.75	65 (1.3)	68 (1.7)	54 (1.7)	49 (1.9)	41 (2.1)	92 (4.9)
0.75–1	75 (1.5)	63 (1.6)	66 (2.0)	45 (1.8)	34 (1.7)	145 (7.8)
Any incident ADL limitation, n	536	390	378	298	259	1,861
Died this wave, n	0	255	239	216	205	915
Did not respond, n	0	157	95	78	94	424

Abbreviation: ADL = activities of daily living.
Percentages may not add to 100% because of rounding.

Table 3 Association between dementia category and incident ADL limitations including interactions between dementia category and individual health factors

	Any ADL limitation	Walking	Dressing	Eating	Getting in/out of bed	Bathing
Physical activity						
Dementia category	1.83 (1.36, 2.46)	1.57 (1.16, 2.14)	2.25 (1.70, 2.98)	2.62 (1.93, 3.56)	1.78 (1.32, 2.39)	2.71 (2.08, 3.54)
Dementia × no physical activity	0.86 (0.63, 1.18)	0.96 (0.70, 1.32)	0.71 (0.53, 0.95)	0.68 (0.49, 0.93)	0.90 (0.65, 1.22)	0.64 (0.48, 0.85)
No physical activity	1.51 (1.25, 1.81)	1.51 (1.15, 2.00)	1.69 (1.35, 2.13)	1.98 (1.39, 2.82)	1.78 (1.32, 2.40)	2.22 (1.69, 2.92)
Drinking						
Dementia category	1.27 (0.88, 1.83)	1.58 (1.10, 2.26)	1.41 (0.95, 2.09)	2.01 (1.43, 2.81)	1.67 (1.17, 2.39)	1.90 (1.39, 2.59)
Dementia × not drinking	1.28 (0.87, 1.87)	0.95 (0.65, 1.39)	1.21 (0.81, 1.81)	0.87 (0.61, 1.23)	0.96 (0.67, 1.38)	0.91 (0.66, 1.26)
Not drinking	1.22 (0.96, 1.56)	1.43 (1.04, 1.97)	1.23 (0.92, 1.65)	1.15 (0.77, 1.73)	1.47 (1.00, 2.17)	1.34 (0.97, 1.85)
Smoking						
Dementia category	1.68 (1.51, 1.86)	1.59 (1.43, 1.77)	1.72 (1.53, 1.92)	1.80 (1.59, 2.03)	1.64 (1.45, 1.85)	1.90 (1.72, 2.11)
Dementia category × smoking	0.99 (0.39, 2.54)	0.87 (0.38, 1.99)	0.61 (0.30, 1.25)	0.34 (0.16, 0.72)	0.68 (0.37, 1.27)	0.50 (0.21, 1.22)
Smoking	1.63 (0.94, 2.82)	1.37 (0.69, 2.71)	1.27 (0.66, 2.41)	2.49 (1.21, 5.13)	2.03 (0.97, 4.28)	2.16 (1.19, 3.92)
Depression						
Dementia category	1.71 (1.51, 1.93)	1.62 (1.43, 1.83)	1.78 (1.57, 2.01)	1.99 (1.74, 2.28)	1.67 (1.47, 1.89)	1.94 (1.72, 2.19)
Dementia × depression	0.72 (0.56, 0.92)	0.89 (0.65, 1.22)	0.78 (0.62, 0.98)	0.74 (0.55, 1.00)	1.05 (0.77, 1.42)	0.89 (0.67, 1.19)
Depression	1.59 (1.27, 2.01)	1.69 (1.31, 2.17)	1.54 (1.21, 1.95)	2.65 (1.91, 3.70)	1.53 (1.14, 2.06)	1.47 (1.14, 1.89)
Income						
Dementia category	1.58 (1.36, 1.82)	1.76 (1.52, 2.04)	1.89 (1.63, 2.19)	2.11 (1.75, 2.55)	1.96 (1.65, 2.32)	2.11 (1.82, 2.45)
Dementia × low income	1.24 (0.91, 1.70)	0.75 (0.55, 1.02)	0.91 (0.71, 1.17)	0.93 (0.71, 1.23)	1.02 (0.77, 1.34)	1.15 (0.87, 1.54)
Low income	0.95 (0.74, 1.23)	1.30 (0.96, 1.75)	0.93 (0.72, 1.21)	1.32 (0.89, 1.96)	1.05 (0.74, 1.49)	0.92 (0.68, 1.23)

Abbreviation: ADL = activities of daily living.
Data are odds ratio (95% confidence interval). We adjusted for the following potential time-constant confounders: age, age squared, sex, race, southern birthplace, education, mother's and father's educations, and height. In addition, we adjusted for the following time-varying confounders using an inverse probability weighting approach: marital status, log of household size–adjusted wealth, body mass index, self-reported comorbidities, interview wave, and our modifiers.

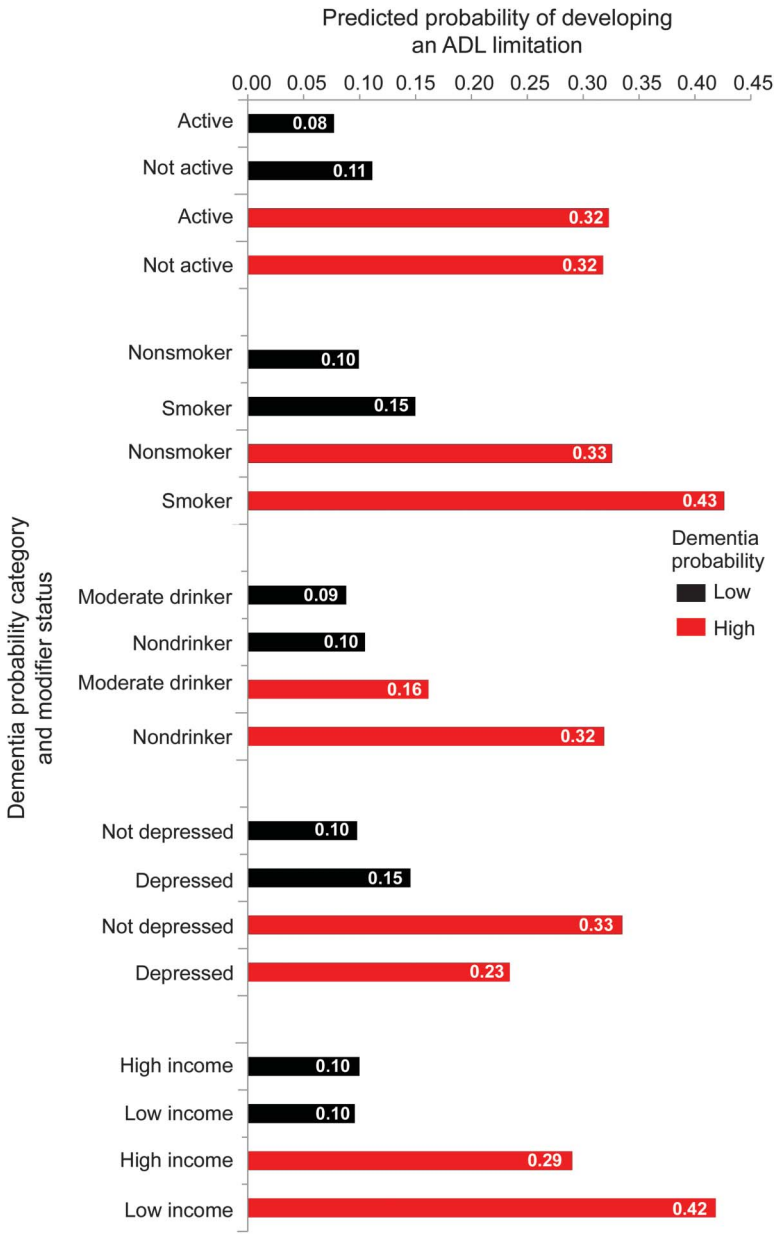
of ADL limitations and the interaction between these modifiers and dementia was also close to the null, suggesting that the relative harm of not drinking, smoking, or low income was similar regardless of dementia probability.

We also calculated the marginal probability of developing any incident ADL limitations for each combination of modifier status and lowest or highest dementia category (figure 2). For example, individuals in the lowest dementia category who are smokers have a 15.0% probability of developing any incident ADL limitation within 2 years. If a similar person is a nonsmoker, the 2-year probability of developing an ADL limitation is only 9.9%, thus not smoking predicts a 5.1 percentage point decrease in the probability of incident ADL limitations among those with low dementia probability. Smokers with the highest dementia scores have a 42.6% chance of developing an ADL limitation within 2 years, but physically active individuals with high dementia probability have only a 32.6% chance of developing any incident ADL limitation within 2 years. Not smoking predicts a 10.0 percentage point decrease in the probability of incident ADL limitations among individuals who are in the highest dementia probability category. Therefore, the absolute effect of not smoking is predicted to be larger among those with higher dementia probability. Not drinking and low income are also predicted to have larger adverse effects on the absolute probability of developing incident ADL limitations among those with high dementia probability than among those with low dementia probability.

DISCUSSION Results from this large prospective cohort study indicate that the relative impact of modifiable risk factors on incident ADL limitations was quite similar for all levels of cognitive functioning. Because disability is more prevalent among individuals with cognitive impairment, some modifiable risk factors had larger absolute benefits for individuals at high risk of dementia. This suggests that even among individuals with substantial cognitive impairment, managing conventional risk factors is very important.

Many of our individual-level modifiers are established predictors of functional decline among healthy elderly, but little evidence exists about whether these

Figure 2 **Marginal predicted probability of any ADL limitation per wave by modifier and dementia status**



Bar lengths represent actual numbers before rounding. Activities of daily living (ADL) limitations were assessed each wave (every 2 years). We adjusted regression models for the following potential confounders: age, age squared, sex, race, southern birthplace, education, mother's and father's educations, and height. In addition, we accounted for the following time-varying confounders using an inverse probability weighting approach: marital status, log of household size–adjusted wealth, body mass index, self-reported comorbidities, interview wave, and our modifiers.

advantages generalize to populations with cognitive impairment.[12] Smoking and depression have repeatedly been linked to disability measures.[13–18] Evidence on alcohol consumption and disability has been mixed.[15,19] Moderate alcohol consumption may have a protective effect for general physical functioning, but high consumption may be harmful.[20] While this study does not specifically assess the impact of initiating alcohol consumption, it suggests that efforts to reduce alcohol consumption may not improve ADL outcomes.

Research has typically focused on the impact of these modifiers on disability or functional limitations among cognitively normal adults,[13,15–17,19] although there is research on the effects of physical activity among those with cognitive impairment. A recent review found that physical activity was beneficial for physical functioning and ADL for mild, moderate, and severe dementia.[21] Some physical activity interventions have also been shown to improve physical functioning in older people with dementia.[22]

Our results on the continuing importance of modifiable risk factors among individuals with cognitive impairments have a great deal of clinical relevance. Conventional risk factors for ADL limitations, such as depression, are often undertreated among those with cognitive impairment.[5] Even traditional vascular risk factors, such as high blood pressure, dyslipidemia, diabetes mellitus, smoking, and atherosclerotic disease, may be untreated in those with cognitive impairment.[23] However, healthy risk factor profiles may help individuals with incipient dementia maintain functional independence, thereby avoiding institutionalization and decreasing caregiver burden.

We hypothesize that cognitive impairment may result in functional limitations through a multistep process. Cognitive function may be most relevant for maintaining independence among individuals with some level of physical impairments, who need to adopt behavioral accommodations or adaptive equipment to maintain independence. Because conventional risk factors delay physical impairments, they are very valuable for delaying dependence among individuals with cognitive impairment. For example, physical activity, smoking, alcohol use, and depression have all been linked to cardiovascular disease and other pathologies. Cognitive losses and conventional risk factors may create unfortunate cascades in which one reinforces the other, ultimately culminating in disability. For example, an individual with cognitive impairment may curtail independent leisure time walks or other physical activity because of safety concerns. Recognition of memory losses may lead to sadness and depression among older adults.

As with all observational research, we cannot rule out unmeasured confounding and therefore cannot infer that the observed effects are causal. Physical impairments may affect the risk factors we examined, thus confounding associations between, for example, physical activity and incident ADL limitations. This study only focused on incident ADL limitations and did not consider instrumental ADL, which may be more strongly correlated with cognition.[24] While the modifiable risk factors may provide ways of

ameliorating the harmful effect of dementia probability, dementia probability is still a strong risk factor for incident ADL limitations. We do not have information on lifetime behavior history and cannot determine whether the beneficial associations are only present among those who have always practiced healthy behaviors. In addition, our measure of depression may not capture differences in depression severity appropriately in individuals with cognitive impairment. Differences in depression severity may be one possible explanation for the unexpected finding that depression may be less harmful, in relative terms, among those with cognitive impairment. We do not know when exactly within the 2-year time period between assessments that the ADL limitation developed. However, we used information on cognitive status and health modifiers from the wave before ADL assessment to avoid reverse causation. Finally, we did not examine disability fluctuations in this study. An exploratory analysis of our data found that those in the highest dementia probability category had lower odds of transitioning out of ADL limitations than those in the lowest dementia probability category. Therefore, by not examining fluctuations in ADL disability, we believe that our results are conservative estimates of the beneficial effects of our health modifiers. Because those with the highest dementia probability are the least likely to transition out of the disability state, preventing the onset of ADL limitations is important.

Among the strengths of this study is that it included a nationally representative sample with a long prospective follow-up; the longitudinal data allowed construction of a statistical model reflecting the hypothesized temporal sequencing of these factors. Given the potential dynamic feedback between cognitive impairment and other risk factors, we used IPW, currently the best available statistical tool to handle time-varying confounders and selective attrition. By using imputed dementia categories, we were able to use information from proxy reports of cognitive status instead of excluding individuals with more severe cognitive impairments. We examined both relative and absolute effects; absolute effect estimates are most relevant for evaluating public health impact.[25]

Smoking, not drinking, and having low income may increase the risk of incident ADL limitations among those with cognitive impairments. This finding has critical importance for clinicians, patients, and family members of individuals with cognitive impairments or incipient dementia. By managing conventional risk factors, it may be possible to stave off dependencies, maximize quality of life, and minimize caregiver burden.

AUTHOR CONTRIBUTIONS

Pamela M. Rist: drafting/revising the manuscript for content, including medical writing for content, study concept or design, and analysis or interpretation of data. Benjamin D. Capistrant, Qiong Wu, and Jessica R. Marden: interpretation of data and revising the manuscript for content. M. Maria Glymour: obtaining funding, study concept or design; interpretation of data, revising the manuscript for content, and supervision.

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REFERENCES

1. Royall DR, Lauterbach EC, Kaufer D, et al. The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2007;19:249–265.
2. Gaugler JE, Kane RL, Kane RA, Clay T, Newcomer R. Caregiving and institutionalization of cognitively impaired older people: utilizing dynamic predictors of change. Gerontologist 2003;43:219–229.
3. Jette AM. Toward a common language for function, disability, and health. Phys Ther 2006;86:726–734.
4. Verbrugge LM, Jette AM. The disablement process. Soc Sci Med 1994;38:1–14.
5. Dorenlot P, Harboun M, Bige V, Henrard JC, Ankri J. Major depression as a risk factor for early institutionalization of dementia patients living in the community. Int J Geriatr Psychiatry 2005;20:471–478.
6. Juster FT, Suzman R. The Health and Retirement Study: an overview. J Hum Resour 1995;30(suppl):7–56.
7. Heeringa SC. Technical Description of the Asset and Health Dynamics (AHEAD) Sample Design. Report of the Survey Design and Analysis Unit. Ann Arbor, MI: Institute for Social Research, University of Michigan; 1995.
8. St. Clair P, Blake D, Bugliari D, et al. RAND HRS Data Documentation. Santa Monica, CA: RAND Center for the Study of Aging; 2010.
9. Wu Q, Tchetgen Tchetgen EJ, Osypuk TL, White K, Mujahid M, Glymour MM. Combining direct and proxy assessments to reduce attrition bias in a longitudinal study. Alzheimer Dis Assoc Disord 2013;27(suppl):207–212.
10. Steffick DE, Wallace RB, Herzog R, Ofstedal MB, Fonda S, Langa K. Documentation of Affective Functioning Measures in the Health and Retirement Study. HRS/AHEAD Documentation Report. Ann Arbor, MI: Survey Research Center, University of Michigan; 2000.
11. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine

on the survival of HIV-positive men. Epidemiology 2000; 11:561–570.
12. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. Soc Sci Med 1999;48:445–469.
13. Eriksen W, Natvig B, Rutle O, Bruusgaard D. Smoking as a predictor of long-term work disability in physically active and inactive people. Occup Med 1998;48:315–320.
14. Haas AL, Eng C, Dowling G, Schmitt E, Hall SM. The relationship between smoking history and current functioning in disabled community-living older adults. Ann Behav Med 2005;29:166–173.
15. Klijs B, Mackenbach JP, Kunst AE. Obesity, smoking, alcohol consumption and years lived with disability: a Sullivan life table approach. BMC Public Health 2011; 11:378.
16. Schmitz N, Kruse J, Kugler J. Smoking and its association with disability in chronic conditions: results from the Canadian Community and Health Survey 2.1. Nicotine Tob Res 2007;9:959–964.
17. Takashima N, Miura K, Hozawa A, et al. Cigarette smoking in middle age and a long-term risk of impaired activities of daily living: NIPPON DATA80. Nicotine Tob Res 2010;12:944–949.
18. Schillerstrom JE, Royall DR, Palmer RF. Depression, disability and intermediate pathways: a review of longitudinal studies in elders. J Geriatr Psychiatry Neurol 2008;21: 183–197.
19. Karlamangla AS, Sarkisian CA, Kado DM, et al. Light to moderate alcohol consumption and disability: variable benefits by health status. Am J Epidemiol 2009;169: 96–104.
20. Oslin DW. Alcohol use in late life: disability and comorbidity. J Geriatr Psychiatry Neurol 2000;13:134–140.
21. Blankevoort CG, van Heuvelen MJ, Boersma F, Luning H, de Jong J, Scherder EJ. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. Dement Geriatr Cogn Disord 2010;30:392–402.
22. Potter R, Ellard D, Rees K, Thorogood M. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. Int J Geriatr Psychiatry 2011;26:1000–1011.
23. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. Neurology 2009;73:674–680.
24. Park DC. Psychological issues related to competence: cognitive aging and instrumental activities of daily living. In: Willis SL, Schaie KW, Hayward M, editors. Societal Mechanisms for Maintaining Competence in Old Age. New York: Springer; 1997:66–80.
25. Szklo MF, Nieto J. Epidemiology: Beyond the Basics. Sudbury, MA: Jones and Bartlett; 2000:408–430.